

Determinants of Asbestos Toxicity

— *Same toxicity for all asbestos types?* —

Fiber Characteristics

— 3 “D’s”

- *dosimetry; which dosimetric?*
- *short vs. long fibers*
- *biopersistence; chrysotile vs. amphiboles*

Environmental Factors

— mixed exposures

- *fibers and non-fibers*
- *different fiber types*

— occupational vs. environmental exposures

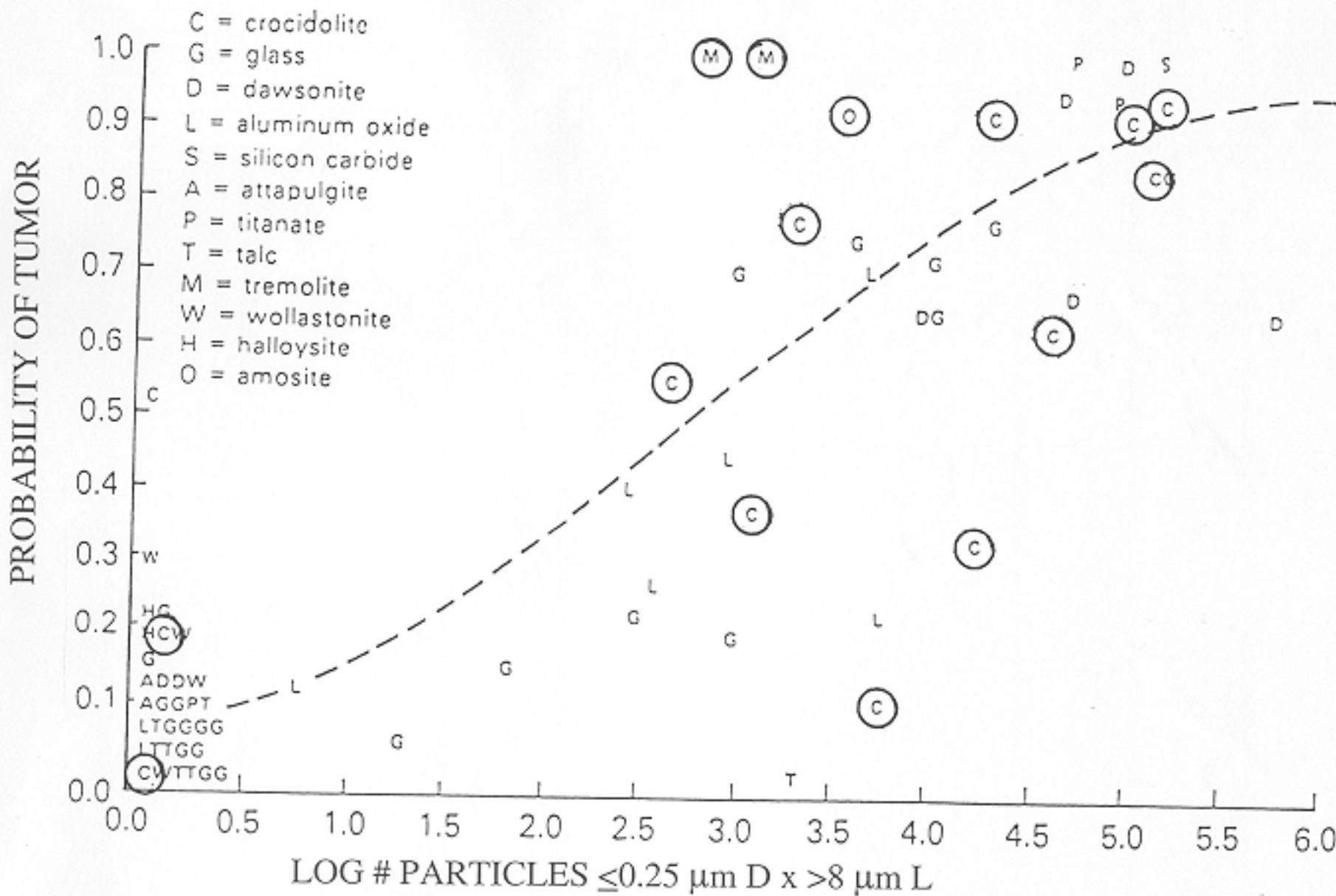
- *cancer, non-cancer effects*

Host Factors

— susceptible populations

- *age*
- *pre-existing conditions*

Stanton *et al.*, 1981: Pleural tumors after 40 mg i.pl. implantation
 Carcinogenicity depends on dimension and durability of fibers:
 durable, long and thin fibers



Intracavitary Injection Studies

Useful for Risk Assessment?

Caveats: High dose per surface area (*inflammation*)

Relevancy for lung tumors? (*diff. cell types; mechanisms*)

Relevancy for mesothelioma? (*fibers have to migrate from alveoli to pleura*)

Intracavitary test will identify:

Potential to induce mesothelioma

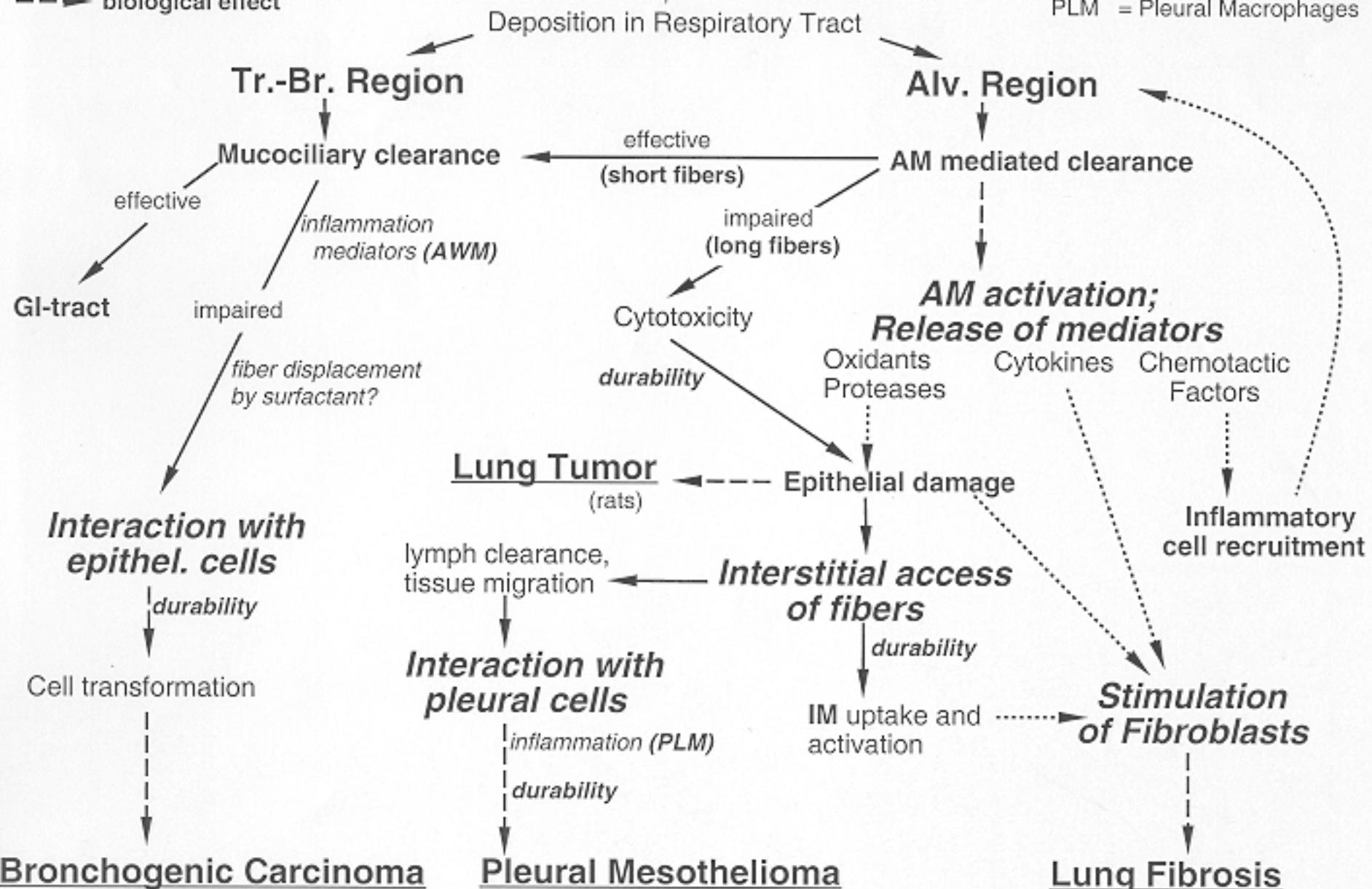
Concepts of fiber toxicology

Pathogenic Sequence for Effects of Asbestos Fibers in the Respiratory Tract

→ movement of fibers
→ response to mediators
→ biological effect

Exposure to Airborne Asbestos

AM = Alveolar macrophages
AWM = Airway Macrophages
IM = Interstitial Macrophages
PLM = Pleural Macrophages



Pathogenicity and Fiber Length: The Role of AM Size

Hypothesis: Phagocytizable fibers → clearance
prevention of target cell interaction

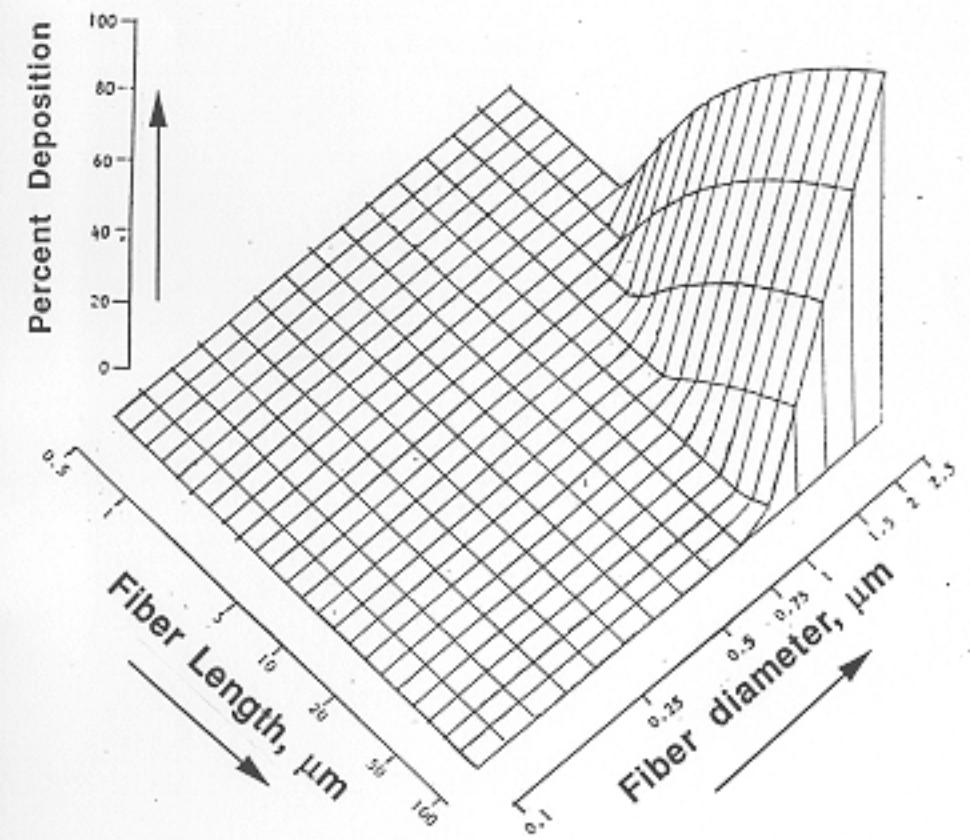
Average AM Diameters:

Rat: 10.5 – 13 µm } Crapo *et al.*, 1983; Lum *et al.*, 1983; Stone *et al.*, 1992;
Human: 14 – 21 µm } Sebring and Lehnert, 1992; Krombach *et al.*, 1997

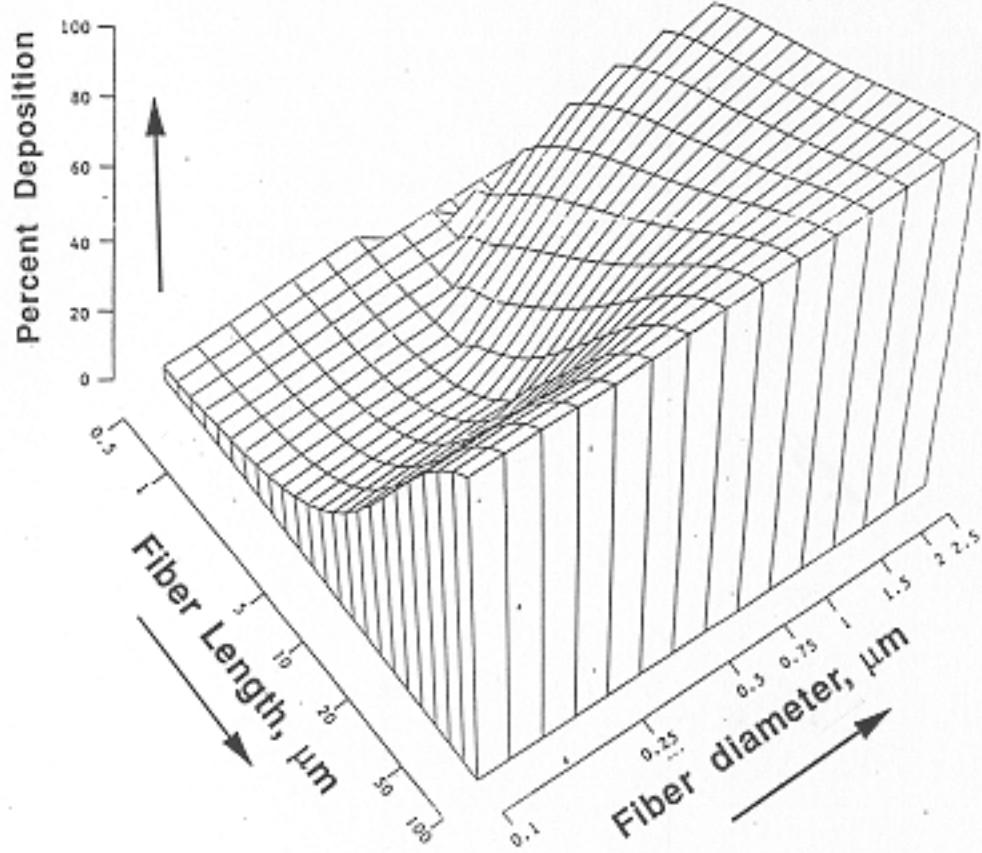
For cancer → number of fibers longer 20 µm

For non-cancer → all fibers (*but: also impact for tumors!*)

Predicted deposition of fibers in human extrathoracic airways
(after Yu, 1990)

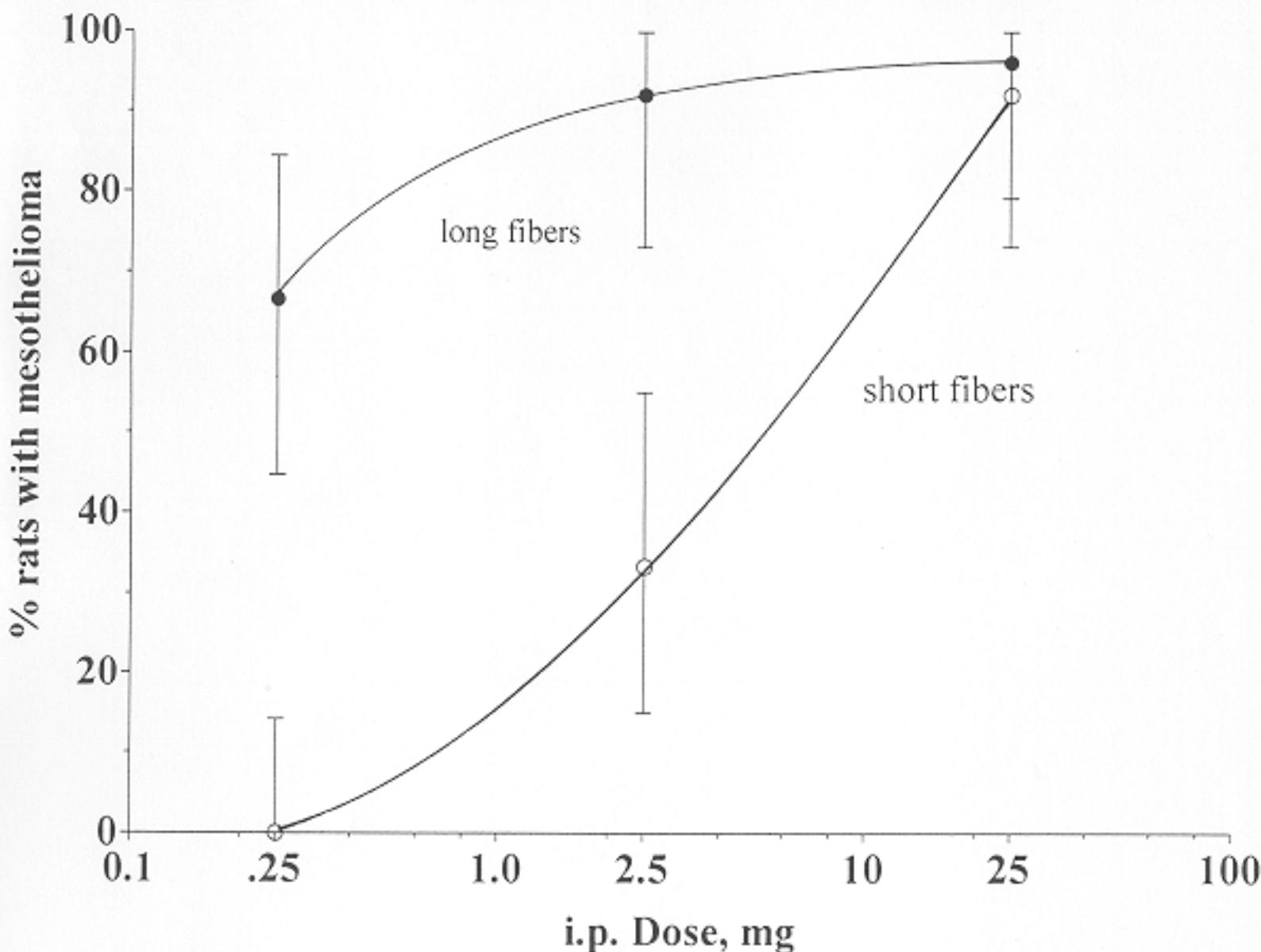


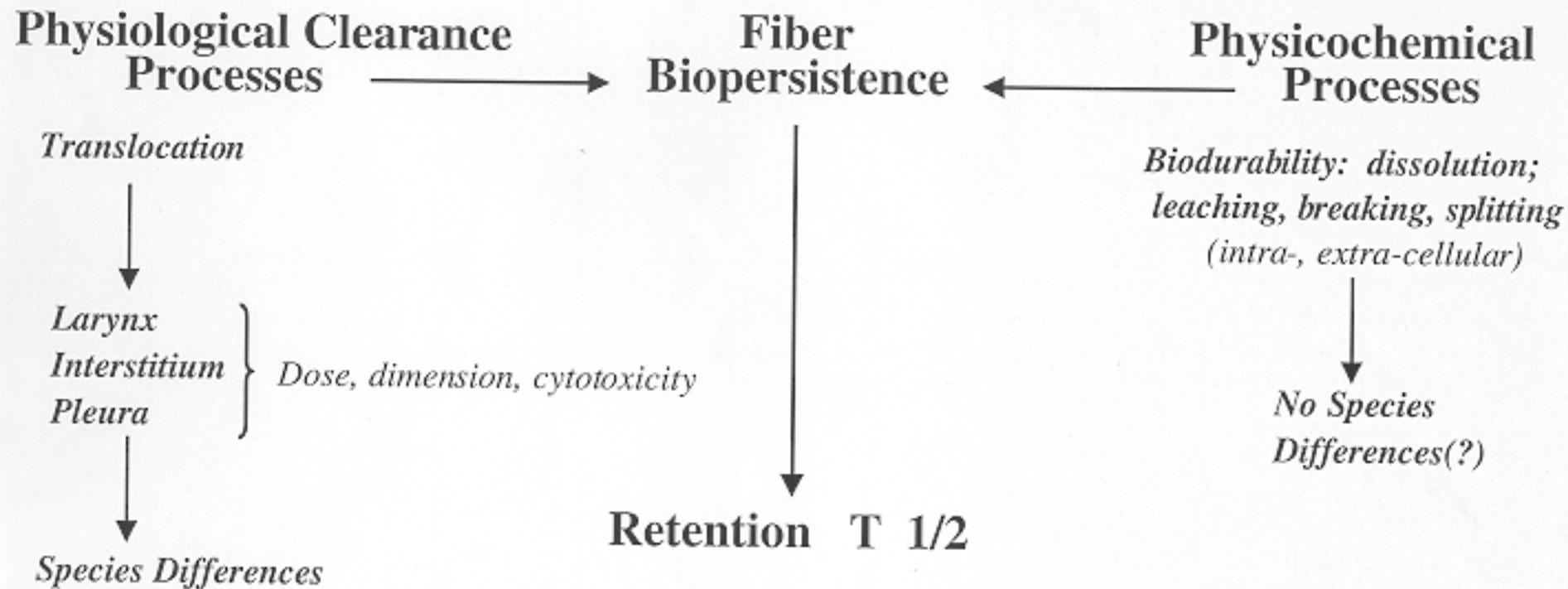
Mouth-breathing



Nose-breathing

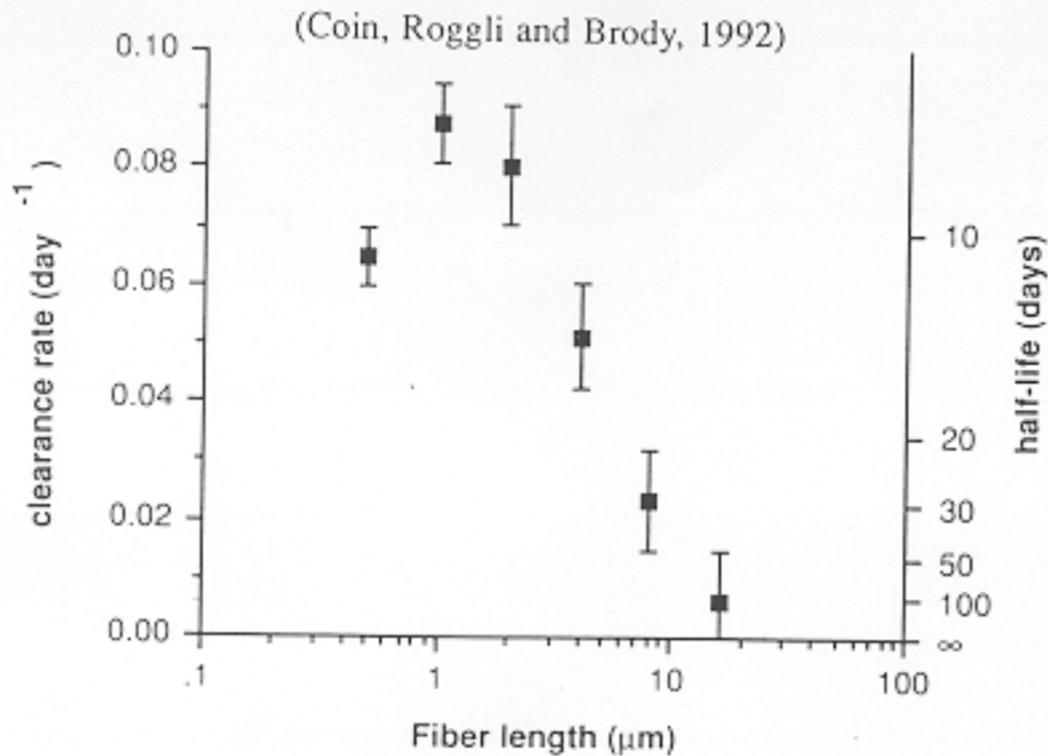
Peritoneal mesothelioma After I.P.
of Long and Short Chrysotile
(mean and 95% CI) (Davis and Jones, 1988)





$$\text{Biopersistence} = \text{Biodurability} + \text{Physiological Clearance}$$

Clearance of Chrysotile from Rat Lung



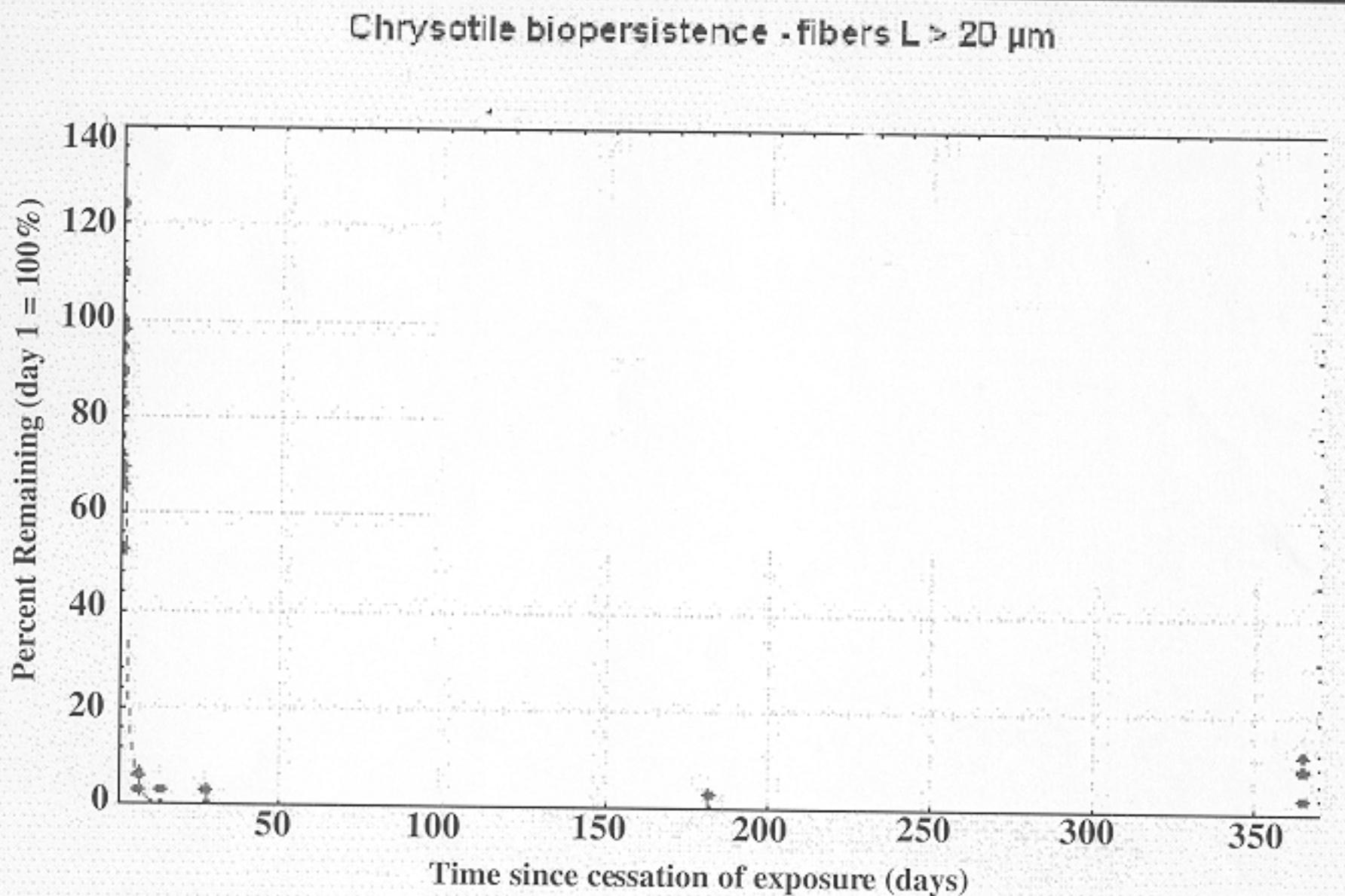
Chronic Inhalation of Asbestos (long fiber studies) in Rats; Effects and Biopersistence

Asbestos Type*	Fibrosis	Lung Tumors	Mesothelioma	T1/2, days
Amosite	+	+	+	>1000
Crocidolite	+	+	+	~1000
Tremolite	+	+	+	like other amphiboles(?)
Anthophyllite	+	+	+	1000 (?)
Chrysotile	+	+	+/-	~2 - 140

*Note: All asbestos types induced mesothelioma in rats following intracavitary injection (pleural, peritoneal) of very high doses (1×10^7 - 1×10^9 fibers, equivalent to a lung dose greater than the weight of the lung)

Biopersistence and Effects of Chrysotile in Rats

Study	Fiber	Biopersistence	Interstitial	Lung	Pleural
	Characteristics		Fibrosis	Tumors	Mesothelioma
Wagner <i>et al.</i> , 74 10 mg/m ³ , 24 mos	Rhodesian	Steady-state	+	+	-
	Canadian	lung burden, no build-up	+	+	+
NTP, 78/79 (McConnell <i>et al.</i> , 82 Pinkerton <i>et al.</i> , 82/84 Ilgren & Chatfield, 97/98) ~8-11 mg/m ³ , 12 mos	UICC-B	Not done (Si-content variable + inconclusive)	+	+	-
	Long (<i>Jeffrey, Quebec</i>)		+	+	-
	Short (<i>Coalinga, CA</i>)		-	-	-
Platek <i>et al.</i> , 85 1 mg/m ³ , 18 mos	Chrysotile, short (JM)	40% clearance <5 µm (6 mo post-expos.)	-	-	-
		no clearance >5 µm (6 mo post-expos.)			
Muhle <i>et al.</i> , 87 6 mg/m ³ , 12 mos	Coalinga (short)	90% clearance within 10 mos	(+)	-	-
Davis & Jones, 88 10 mg/m ³ , 12 mos	"Short"	90% clearance (6 mos post-expos)	(+)	+	-
	Canadian	50% clearance (6 mos post-expos)	+	+	+
	Long				
McConnell <i>et al.</i> , 91 10 mg/m ³ , 12 mos	Jeffrey (<i>Quebec</i>)	not done	+	+	-
Bernstein <i>et al.</i> , 99;00	Brazilian (<i>Cana Brava</i>) (465 f/cm ³ >20 µm)	T1/2=1.3 d >20 µm T1/2=2.4 d >5-20 µm	Abstracts Only	<i>Results Not Yet Published</i>	



ENVIRONMENTAL FACTORS

MIXED DUST EXPOSURES: POTENTIATION OF FIBER EFFECT?

Macrophage function may be affected in additive/synergistic fashion:

- clearance function (*Ferin and Leach, 1976*)
- greater accumulation of fibers (*e.g., smoke + crocid., Muhle et al., 1989; smoke + amosite, Churg et al., 1992*)
- phagolysosomal dissolution affected?
- increased long-term effects
 - amosite or chrysotile \pm SiO_2 or TiO_2 (*Davis et al., 1991*)
 - brucite (9 mg/m³) + chrysotile (1 mg/m³, contaminant) (*Davis et al., 1985*)

Mixed Dust Exposures in Rats (Davis et al., 1991)

Chrysotile or amosite (10 mg/m^3) plus TiO_2 (10 mg/m^3) or quartz (2 mg/m^3),
1-year rat inhalation study plus 2-year observation period

	Fiber retention	Pulm. fibrosis	Transport across visc.	Lung tumors	Mesothelioma	Survival rate
Chrysotile + TiO_2	↑	○	?	↑	↑ ^a	↑
Amosite + TiO_2	○	○	↑	↑	↑	↑
Chrysotile + quartz	↓	↑	?	↑	↑ ^{a,b}	↓
Amosite + quartz	○	↑	↑	↑	↑ ^b	↓

○ no change; ↑ increased; ↓ decreased; (compared to asbestos alone)
(predicted lung burden of TiO_2 in “overload” range, $\sim 10 \text{ mg/lung}$)

^a = no mesothelioma with chrysotile alone

^b = greater effect of added quartz than of added TiO_2

Host Factors for Increased Susceptibility to Asbestos

Compromised respiratory system:

- Synergism smoking and occupational exposures → fibrosis, lung tumors

Diet:

- Lower incidence of asbestos induced lung tumors → dietary restriction study, mice
(Koizumi et al., 1993)

Genetic deficiency:

- GST-mu and NAT deficiency → associated with increased susceptibility
Glutathione-S-Transferase
N-acetyltransferase (Smith, 1994; Hirvonen et al., 1996; Saarikoski et al., 1997)

Experience from PM Studies

(non-carcinogenic effects)

*Association between ambient PM levels and increased morbidity/mortality
from respiratory/cardiovascular disease in compromised people.*

But: *No data for ambient asbestos exposures*

CONCLUSIONS

— Concepts of Asbestos Toxicity —

- Dimension and Biopersistence → most important determinants of toxicity
 - clearance of short vs. long fibers (*AM-mediated vs. epith. cells, translocation*)
 - long ($>20 \mu\text{m}$) and thin ($\sim 0.5 \mu\text{m}$) → more carcinogenic than short fibers
but: short fibers contribute to risk (do not disregard fibers $< 5\mu\text{m}$, especially if clearance is retarded)
 - amphiboles → high biopersistence
 - chrysotile → lower biopersistence, difference between localities?
- Dose and Dosemetric:
 - respirability (*aerodynamic behavior*)
 - fiber number → cancer dosemetric
 - fiber surface area → non-cancer endpoints?

CONCLUSIONS (Con't)

— Concepts of Asbestos Toxicity —

- Rat inhalation studies: amphiboles → fibrosis, lung tumors, mesothelioma
chrysotile → range of responses: locality, contaminants?
- Mixed dust exposures (asbestos + particles) → increased fibrogenic, tumorigenic effects
- Host factors (pre-existing conditions) → increased susceptibility